

## Long Covid – Into the Third Year

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As the COVID-19 pandemic reaches the end of its third year, and as COVID-related mortality in North America wanes, long Covid and its disabling symptoms are attracting more attention. Some individuals report symptoms lasting more than 2 years, and a subset report continuing disability. This article will provide an update on long Covid, with a particular focus on disease prevalence, disability, symptom clustering and risk factors. It will also discuss the longer-term outlook for individuals with long Covid.

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Long Covid describes a complex of symptoms that persist for at least 12 weeks following acute Covid-19 infection.<sup>1,2</sup> As the COVID-19 pandemic reaches the end of its third year, the prevalence of long Covid is still up in the air, despite a profusion of studies over the past year. These studies have provided vastly contrasting figures, ranging from 1%-70%, of Covid-19 survivors.<sup>3-10</sup> Hospital survivors continue to show the highest prevalence; those who have been ventilated, partic-

ularly so.<sup>10</sup> In reports that include both hospitalized and community survivors, prevalence varies between 10%-40%.<sup>3,5,9</sup> For reports limited to community survivors, the prevalence varies from 1%-10%.<sup>6-8</sup> The US Centers for Disease Control reports a prevalence of 20%,<sup>3</sup> the figure that is most cited by media. The reasons for the wide prevalence ranges are multiple: different cohorts under study, different methodologies, different definitions of long Covid, different pandemic study periods,

different viral variants, different vaccine status, and so on. At this point, the current estimates may be as close to the truth that we can get. More accurate estimates await an improved characterization of long Covid, both clinical and mechanistic. Such characterization will remove many of the impediments to accurate counting and should bring the correct figure towards the lower end of present estimates.

### HOW MANY ARE DISABLED?

Amongst individuals with long Covid symptoms, some percentage is either unable to work or obliged to reduce their working hours. As the prevalence of long Covid is uncertain, the number of disabled remains a matter of conjecture, as it is frequently expressed as a percentage of the former. An early report, based on an online survey, suggested that 23% of long Covid individuals were unable to work at 7 months, and 45% had a reduced workload.<sup>11</sup> The UK Office for National Statistics reported that the day-to-day activities of 21% of those with long Covid had been “limited a lot,” but it is unclear how many of these were not working or were receiving unemployment benefits.<sup>12</sup> The absolute numbers of disabled due to long Covid are nonetheless impressive. Using the lower estimate of 25% disability, 2 million Americans could be disabled due to long Covid, increasing to 4 million with the higher estimate. Equivalent figures for the UK would be 380,000 to 1.3M and approximately 250,000 to 800,000 for Canada.

### HOW DO THE NUMBERS RELATE TO DISABILITY INSURANCE?

Insured populations are younger and healthier. They are less likely to have had severe Covid-19 and less likely to have been hospitalized. They are also more likely to be vaccinated. Thus, the risk of disabling long Covid is reduced (see risk factors below). So, despite the impressive general population

numbers described above, insured populations should report lower levels of disability. Indeed, informal reports from insurers in multiple jurisdictions support this observation: disability claims for long Covid have been relatively few. Admittedly, this trend could be reversed by a variant with increased virulence, but at this point in the pandemic, it appears that the impact on disability insurance has been limited.

### RISK FACTORS

Hospitalization, and in particular admission to an intensive care unit, are clear risk factors for long Covid.<sup>10,13</sup> The risk factors in the non-hospitalized have become clearer, following 4 large UK retrospective cohort analyses published in 2022.<sup>6,8,13,14</sup> The most recent of these examined a large primary care database that included 486,149 adults with a confirmed SARS-CoV-2 infection.<sup>9</sup> When compared with 1,944,580 propensity-matched controls, the risk factors for long Covid at 12 weeks were: decreasing age, female sex, smoking, lower socioeconomic status, non-white ethnicity and a variety of comorbidities. Interestingly, diabetes, hypertension and cardiovascular disease did not feature amongst these, in contrast to earlier studies.

The examination of large population databases provides a more accurate tabulation of risk factors than self-reports. Shortcomings remain, however, as databases do not include those with long Covid symptoms who did not seek care. Further, subjects with an undocumented or asymptomatic Covid-19 infection may be incorrectly assigned to a control group. Both will lead to underreporting of long Covid symptoms and could invalidate a risk factor analysis. However, the sheer size of these more recent studies and the efforts expended to adjust for design shortcomings have improved the tabulation of risk factors.

Two further risk factors merit a mention: viral variants and vaccination status. A UK group reported a 25%-50% reduction in the

odds of long COVID following omicron, as compared to delta infection, varying with age, and time since vaccination.<sup>15</sup> Generalization of these results is problematic for two reasons: first, the study was based on self-reporting to an online app and thus unlikely to reflect a general population. Second, during the study period (December 2021- March 2022) the BA.1 omicron variant was prevalent. Subsequent omicron variants demonstrated higher infectivity. As Covid-19 infection is the sine qua non of long Covid, it is possible that long Covid incidence will also increase.

The unvaccinated face a higher risk of long Covid. Vaccination protects against severe Covid-19 infection, preventing hospitalization and admission to critical care units, both major determinants of long Covid. However, vaccination does not prevent all Covid-19 infections. Further, its efficacy varies by viral variant, and the immunity it provides wanes over time. Thus, breakthrough infection (BTI) is common. When compared to Covid-19 infection in the unvaccinated, reports suggest that the likelihood of long Covid symptoms following BTI may be reduced by as much as 50%.<sup>16-18</sup> In spite of early reports that vaccination may reduce the duration of long Covid symptoms, the evidence for this is tenuous.<sup>19</sup>

### **CLINICAL PICTURE IS NO CLEARER, BUT CLUSTERS EMERGE**

The multiplicity of symptoms reported by long Covid patients provides a staggering challenge for both clinicians and researchers. It is almost certain that amongst these many symptoms discrete clinical entities exist. Some of these, such as post-viral fatigue syndrome and chronic fatigue syndrome/myalgic encephalitis are already familiar. But a brand-new long Covid entity may also emerge, with a unique clinical profile and well-defined pathophysiology. Further, there may be subtypes of this new long Covid entity, each with different risk factors and time courses.

Symptom clusters are now emerging. A recent preprint reported the clustering results in

24 publications of long Covid symptoms.<sup>14</sup> It noted that while up to 8 clusters have been identified, 3 tended to recur. A cardiopulmonary cluster was the most common. The symptoms in this cluster were dyspnea, exercise intolerance, fatigue, autonomic dysfunction, palpitations, and chest pain. A neurological or neuropsychiatric cluster was the second. It included brain fog, memory or cognitive complaints, headache, chronic pain or myalgias, and mood disorder. A persistent autoimmune activation cluster was the third. It included fever, gastrointestinal and dermatological symptoms. The same study analyzed the symptom profile among 9,323 long Covid individuals across different viral variants (other than Omicron) and different immunization status. It identified a cardiovascular and neurological cluster common to all variants in addition to a third described as a “multi-organ symptom” cluster, that included the most severe cases. Cluster segregation and frequency did not alter with different vaccination profiles.

Clustering exercises are useful when attempting to elucidate disease mechanisms. For example, a cluster of neurological symptoms suggests that, in a defined cohort, cerebral function is awry. This has prompted the hypothesis that neuroinflammation or neurovascular damage may be culprit mechanisms. Similarly, the cardiorespiratory symptoms suggest residual or ongoing lung or heart disease. Pulmonary and/or cardiac inflammation or fibrosis may be plausible explanations for these. Clusters also help to anticipate clinical course and develop rehabilitation interventions adapted to individual patients.

### **LONGER-TERM OUTLOOK**

The natural history of long Covid is unclear. However, it appears that symptoms improve over time, for many, if not most. A recent study of 1.2 million Covid-19 survivors reported a 6% prevalence of a defined symptom

cluster at 3 months, (clusters were “persistent fatigue with pain or mood swings,” “respiratory problems,” and “cognitive problems”) reducing to 0.9% at 1 year.<sup>9</sup> The estimated mean duration of a cluster of symptoms was 9 months amongst those hospitalized, and 4 months amongst community survivors. A smaller French study reported that 85% of individuals still reported symptoms at 12 months, but the study cohort was self-selected, and limited to those who were test-positive, making comparison difficult.<sup>20</sup>

A further question arises at this point: do individuals with long Covid symptoms experience increased long-term morbidity? A recent study of American veterans with long Covid symptoms suggested that incident diabetes is more common, particularly amongst those who were hospitalised.<sup>21</sup> Other studies, not limited to individuals with long Covid symptoms, have demonstrated an increased incidence of cardiovascular, thromboembolic and neurological events at 1 year, in Covid-19 survivors.<sup>22-25</sup> While it is likely that these studies included many individuals with long Covid symptoms, they were not analyzed separately. Thus, the extrapolation to long Covid individuals is problematic. Further, as these studies were based on the examination of electronic health records in selected cohorts, cautious interpretation is needed.

## CONCLUSION

At the end of the third year of the Covid-19 pandemic, long Covid continues to pose multiple challenges. The multiplicity of descriptors, the lack of consensus definition, and the overlap with well-established entities are but some of these. Prevalence estimates continue to vary considerably as do estimates of disability, but the impact on insurers’ disability portfolios, to date, appears modest. The emergence of well-defined symptom clusters should facilitate both basic and clinical research initiatives. The long-term outlook for most long Covid individuals is a gradual recovery; nevertheless, many individuals con-

tinue to report symptoms after 3 years. It is unclear whether the incidence of diabetes and other chronic illnesses is increased, although preliminary evidence suggests this might be so. Given that at the time of writing multiple new variants with immune escape properties continue to emerge, it is evident that the Covid-19 pandemic is not over. Long Covid will remain a substantial preoccupation for the foreseeable future.

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